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EXAMINER
FORMAN, BETTY J

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/576,715	Applicant(s) HATAKEYAMA, KAZUHISA
	Examiner BJ Forman	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. This action is in response to papers filed 28 May 2002 in Paper No. 19 in which claims 1, 3-8, 10 and 13 were amended, claims 11 and 12 were canceled and claims 14 and 15 were added. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 17 dated 25 January 2002 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejections of Claims 1-8 and 10 under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) are maintained in view of the fact that amendments to the claims introduce new matter which is not supported by the specification. New grounds for rejection necessitated by the amendments are discussed.

Currently claims 1-8, 10 and 13-15 are under prosecution.

Specification

2. The amendment filed 28 May 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment introduces the limitation "sequence-non-specific" into independent Claim 1 (from which Claims 2-8 and 10 depend); independent Claims 13-15;and dependent Claims 3-8. Applicant points to page 6, lines 16-22 for support for the newly added limitation. However, this passage defines the claimed double-stranded DNA-binding protein as "a protein

which binds to chromosome of eukaryote or that of prokaryote strongly and concerns retention of higher-order structure of chromosome....a protein having function to stabilize a complementary double-stranded DNA." This passage does not limit the double-stranded DNA-binding protein to a "sequence-non-specific" double-stranded DNA-binding protein as newly claimed. The specification teaches specific double-stranded DNA-binding protein on pages 13-14, but this teaching does not provide the support for the newly claimed "sequence-non-specific double-stranded DNA-binding protein."

Additionally, the amendment introduces the limitation ""said gene analysis comprising...mapping gene location.....detecting mismatch and complete match" into independent Claim 1 (from which Claims 2-8 and 10 depend). Applicant does not point to support for the newly added limitation. The specification teaches detecting deleted regions (page 18, line 26), the presence or absence of a mutation (page 19, lines 15-17), giant genome mapping (page 19, lines 24-25), and detecting nucleotide sequence (page 18, line 19). However, the specification does not provide support for the newly added "mapping gene location" and "detecting mismatch and complete match".

As such, the amendments introduce new matter into the specification which is not supported by the original specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-8, 10 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed methods are not described in the instant disclosure, claims 1-8, 10 and 13-15 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

The recitation "sequence-non-specific double-stranded DNA-binding protein" is added to the newly amended independent Claim 1 (from which Claims 2-8 and 10 depend); independent Claims 13-15; and dependent Claims 3-8. However, the specification fails to define or provide any disclosure to support such claim recitation. Applicant points to page 6, lines 16-22 for support for the newly added limitation. However, this passage defines the claimed double-stranded DNA-binding protein as "a protein which binds to chromosome of eukaryote or that of prokaryote strongly and concerns retention of higher-order structure of chromosome....a protein having function to stabilize a complementary double-stranded DNA." This passage does not limit the double-stranded DNA-binding protein to a "sequence-non-specific" double-stranded DNA-binding protein as newly claimed. The specification teaches specific double-stranded DNA-binding protein on pages 13-14, but this teaching does not provide the support for the newly claimed "sequence-non-specific double-stranded DNA-binding protein."

Additionally, the recitation "said gene analysis comprising...mapping gene location.....detecting mismatch and complete match" is added to newly amended independent Claim 1 (from which Claims 2-8 and 10 depend). However, the specification fails to define or provide any disclosure to support such claim recitation. Applicant does not point to support

for the newly added limitation. The specification teaches detecting deleted regions (page 18, line 26), the presence or absence of a mutation (page 19, lines 15-17), giant genome mapping (page 19, lines 24-25), and detecting nucleotide sequence (page 18, line 19). However, the specification does not provide support for the newly added "mapping gene location" and "detecting mismatch and complete match".

As such, the specification does not provide support for the newly amended claims.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following rejections are reiterated from the previous Office Action of Paper No.17. These rejections are maintained in view of the fact that the newly added limitation "sequence-non-specific" is deemed new matter.

6. Claims 1, 2 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Weininger et al. (U.S. Patent No. 5,871,902, issued 16 February 1999).

Regarding Claim 1, Weininger et al. disclose a method of gene analysis by detecting hybridization between a probe nucleic acid (PNA) and a sample nucleic acid (TNA) comprising a target sequence (TBR) complementary to that of the probe nucleic acid comprising: immobilizing either the probe nucleic acid or the sample nucleic acid; adding the other probe or sample nucleic acid to the immobilized nucleic acid wherein either the probe or sample nucleic acid is labeled; performing hybridization in the presence of a double-stranded DNA-binding protein having the function to stabilize a complementary double-stranded DNA; and detecting the label to thereby detect hybridization of the probe and sample nucleic acid (Claim 2) wherein the label is fluorescent substance (Column 1, lines 26-33) and wherein gene analysis is performed via the method i.e. the TNA comprise foreign genes, defective genes (Column 17, lines 45-54).

Regarding Claim 2, Weininger et al. disclose the method wherein the sample nucleic acid is DNA (Column 9, lines 43-44).

Regarding Claim 13, Weininger et al. disclose a kit for detecting hybridization between a probe and sample nucleic acid comprising a double-stranded DNA-binding protein (Claim 32). The claim is drawn to a kit comprising a double-stranded DNA-binding protein having the function to stabilize a complementary double-stranded DNA. The intended use of the kit i.e. "for detecting hybridization ... according to the method of Claim 1" is not given any patentable weight. The courts have stated that a preamble is generally not accorded any patentable weight where it merely recites the intended use, and where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone (see *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d at 152, 88 USPQ at 481). In the instant case, the preamble is not accorded any

patentable weight because it merely recites the intended use for the kit and because the components of the kit i.e. a double-stranded DNA-binding protein having the function to stabilize a complementary double-stranded DNA, is able to stand alone and is capable of performing the intended use. Weininger et al. disclose the kit as claimed.

Response to Arguments

7. Applicant argues that Weininger et al teach sequence-specific double-stranded DNA binding proteins and not the newly claimed sequence-non-specific binding proteins. The argument has been considered but is deemed moot in view of the fact that the newly added limitation is considered new matter.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 3-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Weininger et al. (U.S. Patent No. 5,871,902, issued 16 February 1999) in view of Guagliardi et al. (Journal of Molecular Biology, 1997, 267: 841-848) and SwissProt (Accession No. 059631, 15 December 1998 and Accession No. P39476; P81550, 1 February 1995).

Regarding Claim 3, Weininger et al. teach a method of gene analysis by detecting hybridization between a probe nucleic acid (i.e. PNA) and a sample nucleic acid (i.e. TNA) comprising a target sequence (i.e. TBR) complementary to that of the probe nucleic acid comprising: immobilizing either the probe nucleic acid or the sample nucleic acid; adding the other probe or sample nucleic acid to the immobilized nucleic acid wherein either the probe or

sample nucleic acid is labeled; performing hybridization in the presence of a double-stranded DNA-binding protein (i.e. TBA) having the function to stabilize a complementary double-stranded DNA; and detecting the label to thereby detect hybridization of the probe and sample nucleic acid (Claim 2) wherein the label is fluorescent substance (Column 1, lines 26-33) and wherein gene analysis is performed via the method i.e. the TNA comprise foreign genes, defective genes (Column 17, lines 45-54) and wherein the double-stranded DNA-binding protein (i.e. TBA) is selected for optimization of stability (Column 9, lines 47-63) but the do not teach the DNA-binding protein is derived from a hyperthermophilic bacterium. However, hyperthermophilic bacteria were known in the art at the time the claimed invention was made a taught by Guagliardi et al. who teach a similar method of gene analysis comprising: hybridizing a probe nucleic acid and sample nucleic acid in the presence of a double-stranded DNA binding protein derived from a hyperthermophilic bacterium and detecting the hybridization (page 842, Fig. 1) wherein said protein stabilizes complementary double-stranded DNA and promotes hybridization (Abstract) and wherein the promotion of hybridization is "strictly homology dependent" whereby a single mismatch "severely reduces hybridization efficiency" (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to DNA-binding protein of Weininger et al. with the DNA-binding protein derived from a hyperthermophilic bacterium of Guagliardi et al. to thereby differentiate between perfect-match and single mismatch hybridizations as taught by Guagliardi et al. for the obvious benefit of differentiating and detecting single-base mismatches known to be associated with clinically important diseases e.g. sickle cell anemia.

Regarding Claim 4, Guagliardi et al. teach the method wherein the double-stranded DNA-binding protein is derived from an archaebacterium (page 841, right column, first full paragraph).

Regarding Claim 5, Guagliardi et al. teach the method wherein the double-stranded DNA-binding protein is derived from a bacterium belonging to the genus *Sulfolubus* (page 841, right column, first full paragraph).

Regarding Claim 6, Guagliardi et al. teach the method wherein the double-stranded DNA-binding protein is derived from *Sulfolubus solfataricus* (page 841, right column, first full paragraph).

Regarding Claim 7, Guagliardi et al. teach the method wherein the double-stranded DNA-binding protein is the Sso7d protein derived from *Sulfolubus solfataricus* (page 841, right column, first full paragraph).

Regarding Claim 8, Guagliardi et al. teach the sequence of the Sso7d is known (page 841, right column, lines 9-18) and SwissProt specifically teaches the sequence accession No. 059631; P39476; and P81550).

Regarding Claim 10, Weininger et al. teach the method wherein the target nucleic acid is detected with accuracy even in the presence of closely related but different sequences (Column 1, lines 9-13) but they do not specifically teach the amount of the sample is analyzed based on the intensity of a hybridization signal. However, Guagliardi et al. teach the similar method wherein the amount of target sequence is analyzed i.e. the intensity of the labeled nucleic acids bound and unbound to the DNA-binding proteins is analyzed to determine the amount of nucleic acids bound (% annealed product) (page 844, Fig. 2b and page 845, Fig. 3a and Fig. 4a). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detection of Weininger et al. and to analyze the amount target based on the intensity of signal produced as taught by Guagliardi et al. to thereby identify samples having the highest homology to a probe having a disease-specific sequence for the expected benefit of accurately identifying and diagnosing the disease as taught by Guagliardi et al. (page 847, right column, lines 6-14).

Response to Arguments

10. Applicant argues that because Weininger et al do not teach sequence-non-specific DNA binding-proteins, the combination of Weininger et al and Guagliardi et al and SwissProt fails to teach or suggest all limitation of the claims. The argument has been considered but is not found persuasive because Guagliardi et al teach that the DNA binding of their DNA-binding is "strictly homology dependent" (Abstract) and hence it is sequence dependent. Therefore, the combination of Weininger et al and Guagliardi et al and SwissProt teach and suggest every limitation of the claims.

11. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guagliardi et al. (M. Mol. Bio. 1997, 267: 841-848) in view of Stratagene (catalog, 1988, page 39). The claim is drawn to a kit comprising a double-stranded DNA-binding protein having the function to stabilize a complementary double-stranded DNA. The intended use of the kit i.e. "for detecting hybridization ... according to the method of Claim 1" is not given any patentable weight. The courts have stated that a preamble is generally not accorded any patentable weight where it merely recites the intended use, and where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone (see *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d at 152, 88 USPQ at 481). In the instant case, the preamble is not accorded any patentable weight because it merely recites the intended use for the kit and because the components of the kit i.e. a double-stranded DNA-binding protein having the function to stabilize a complementary double-stranded DNA, is able to stand alone and is capable of performing the intended use.

Regarding Claim 13, Guagliardi et al. teach the claimed reagents for detecting hybridization between a probe nucleic acid and a sample nucleic acid comprising: a target sequence complementary to the probe nucleic acid and a double-stranded DNA-binding protein which functions to stabilize complementary double-stranded DNA (page 482, Fig. 1) but they do not teach the reagents combined into a kit. Stratagene catalog teaches a motivation to

combine reagents into kit format (page 39). It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Guagliardi et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. 2) The other service provided in a kit is quality control" (page 39, column 1).

NEW REJECTIONS NECESSITATED BY AMENDMENT

12. Claims 1-8 and 10 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Weininger et al. (U.S. Patent No. 5,871,902, issued 16 February 1999) in view of Guagliardi et al. (Journal of Molecular Biology, 1997, 267: 841-848) and SwissProt (Accession No. 059631, 15 December 1998 and Accession No. P39476; P81550, 1 February 1995).

Regarding Claim 1, Weininger et al. teach a method of gene analysis by detecting hybridization between a probe nucleic acid (PNA) and a sample nucleic acid (TNA) comprising a target sequence (TBR) complementary to that of the probe nucleic acid comprising: immobilizing either the probe nucleic acid or the sample nucleic acid; adding the other probe or sample nucleic acid to the immobilized nucleic acid wherein either the probe or sample nucleic acid is labeled; performing hybridization in the presence of a double-stranded DNA-binding protein having the function to stabilize a complementary double-stranded DNA; and detecting the label to thereby detect hybridization of the probe and sample nucleic acid (Claim 2) wherein

the label is fluorescent substance (Column 1, lines 26-33) and wherein gene analysis is performed comprising the steps of detecting nucleic acid sequence of the sample i.e. detection and differentiation of sample nucleic acids (Column 5, lines 25-33) but they do not teach the DNA-binding protein is sequence-non-specific. However, sequence-non-specific DNA-binding proteins were well known in the art at the time the claimed invention was made as taught by Guagliardi et al. who teach a similar method of gene analysis comprising: hybridizing a probe nucleic acid and sample nucleic acid in the presence of a double-stranded DNA binding protein wherein the protein is sequence-non-specific i.e. strictly dependent on homology (Abstract) wherein said protein stabilizes complementary double-stranded DNA and promotes hybridization (Abstract) and whereby a single mismatch "severely reduces hybridization efficiency" (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to DNA-binding protein of Weininger et al. with the sequence-non-specific DNA-binding protein of Guagliardi et al. to thereby differentiate between perfect-match and single mismatch hybridizations as taught by Guagliardi et al. for the obvious benefit of differentiating and detecting single-base mismatches known to be associated with clinically important diseases e.g. sickle cell anemia.

Regarding Claim 2, Weininger et al. teach the method wherein the sample nucleic acid is DNA (Column 9, lines 43-44).

Regarding Claim 3, Weininger et al. teach the method wherein the double-stranded DNA-binding protein (i.e. TBA) is selected for optimization of stability (Column 9, lines 47-63) but the do not teach the DNA-binding protein is derived from a hyperthermophilic bacterium. However, hyperthermophilic bacteria were known in the art at the time the claimed invention was made a taught by Guagliardi et al. who teach a similar method of gene analysis comprising: hybridizing a probe nucleic acid and sample nucleic acid in the presence of a double-stranded DNA binding protein derived from a hyperthermophilic bacterium and detecting the hybridization (page 842, Fig. 1) wherein said protein stabilizes complementary

double-stranded DNA and promotes hybridization (Abstract) and wherein the promotion of hybridization is "strictly homology dependent" whereby a single mismatch "severely reduces hybridization efficiency" (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to DNA-binding protein of Weininger et al. with the DNA-binding protein derived from a hyperthermophilic bacterium of Guagliardi et al. to thereby differentiate between perfect-match and single mismatch hybridizations as taught by Guagliardi et al. for the obvious benefit of differentiating and detecting single-base mismatches known to be associated with clinically important diseases e.g. sickle cell anemia.

Regarding Claim 4, Guagliardi et al. teach the method wherein the double-stranded DNA-binding protein is derived from an archaebacterium (page 841, right column, first full paragraph).

Regarding Claim 5, Guagliardi et al. teach the method wherein the double-stranded DNA-binding protein is derived from a bacterium belonging to the genus *Sulfolubus* (page 841, right column, first full paragraph).

Regarding Claim 6, Guagliardi et al. teach the method wherein the double-stranded DNA-binding protein is derived from *Sulfolubus solfataricus* (page 841, right column, first full paragraph).

Regarding Claim 7, Guagliardi et al. teach the method wherein the double-stranded DNA-binding protein is the Sso7d protein derived from *Sulfolubus solfataricus* (page 841, right column, first full paragraph).

Regarding Claim 8, Guagliardi et al. teach the sequence of the Sso7d is known (page 841, right column, lines 9-18) and SwissProt specifically teaches the sequence accession No. 059631; P39476; and P81550).

Regarding Claim 10, Weininger et al. teach the method wherein the target nucleic acid is detected with accuracy even in the presence of closely related but different sequences (Column 1, lines 9-13) but they do not specifically teach the amount of the sample is analyzed

based on the intensity of a hybridization signal. However, Guagliardi et al. teach the similar method wherein the amount of target sequence is analyzed i.e. the intensity of the labeled nucleic acids bound and unbound to the DNA-binding proteins is analyzed to determine the amount of nucleic acids bound (% annealed product) (page 844, Fig. 2b and page 845, Fig. 3a and Fig. 4a). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detection of Weininger et al. and to analyze the amount target based on the intensity of signal produced as taught by Guagliardi et al. to thereby identify samples having the highest homology to a probe having a disease-specific sequence for the expected benefit of accurately identifying and diagnosing the disease as taught by Guagliardi et al. (page 847, right column, lines 6-14).

Regarding Claim 14, teach a method of gene analysis by detecting hybridization between a plurality of probe nucleic acids (Column 12, lines 1-6) (PNA) and a sample nucleic acid (TNA) comprising a target sequence (TBR) complementary to that of the probe nucleic acid comprising: immobilizing either the plurality of probe nucleic acids or the sample nucleic acid; adding the other probe or sample nucleic acid to the immobilized nucleic acid wherein either the probe or sample nucleic acid is labeled; performing hybridization of the plurality of probe nucleic acids and sample nucleic acids in the presence of a double-stranded DNA-binding protein having the function to stabilize a complementary double-stranded DNA; and detecting hybridization from the presence of the label to thereby detect nucleic acid sequence of the sample i.e. detection and differentiation of sample nucleic acids (Column 5, lines 25-33) but they do not specifically teach detection of a polymorphism and they do not teach the DNA-binding protein is sequence-non-specific. However, polymorphism detection using sequence-non-specific DNA-binding proteins were well known in the art at the time the claimed invention was made as taught by Guagliardi et al. who teach a similar method of gene analysis comprising: hybridizing a probe nucleic acid and sample nucleic acid in the presence of a double-stranded DNA binding protein wherein the protein is sequence-non-specific i.e. strictly

dependent on homology wherein said protein stabilizes complementary double-stranded DNA and promotes hybridization and whereby a single mismatch "severely reduces hybridization efficiency" (Abstract) and detecting the polymorphism in the target sequence by comparing the hybridization signal obtained from the hybridization (page 844, right column, first paragraph and page 845, Fig. 4) and wherein the intensity of each hybridization signal is obtained and compared (page 845, Fig. 4, and page 842, Fig. 1). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to DNA-binding protein of Weininger et al. with the sequence-non-specific DNA-binding protein of Guagliardi et al. to thereby differentiate between perfect-match and single mismatch hybridizations e.g. polymorphisms as taught by Guagliardi et al. for the obvious benefit of differentiating and detecting single-base mismatches known to be associated with clinically important diseases e.g. sickle cell anemia.

Regarding Claim 15, Weininger teach a method of gene analysis by detecting hybridization between a plurality of probe nucleic acids (Column 12, lines 1-6) (PNA) and a sample nucleic acid (TNA) comprising a target sequence (TBR) complementary to that of the probe nucleic acid comprising: immobilizing either the probe nucleic acid or the sample nucleic acid; adding the other probe or sample nucleic acid to the immobilized nucleic acid wherein either the probe or sample nucleic acid is labeled; performing hybridization in the presence of a double-stranded DNA-binding protein having the function to stabilize a complementary double-stranded DNA; and detecting the label to thereby detect hybridization of the probe and sample nucleic acid (Claim 2) wherein the label is fluorescent substance (Column 1, lines 26-33) and detecting nucleic acid sequence of the sample i.e. detection and differentiation of sample nucleic acids (Column 5, lines 25-33) but they do not specifically teach the intensity of each hybridization signal and they do not teach the DNA-binding protein is sequence-non-specific. However, sequence-non-specific DNA-binding proteins were well known in the art at the time the claimed invention was made as taught by Guagliardi et al. who teach a similar method of

gene analysis comprising: hybridizing a probe nucleic acid and sample nucleic acid in the presence of a double-stranded DNA binding protein wherein the protein is sequence-non-specific i.e. strictly dependent on homology wherein said protein stabilizes complementary double-stranded DNA and promotes hybridization and whereby a single mismatch "severely reduces hybridization efficiency" (Abstract) and detecting nucleotide sequence by comparing the hybridization signal (page 844, right column, first paragraph and page 845, Fig. 4) and wherein the intensity of each hybridization signal is obtained and compared (page 845, Fig. 4, and page 842, Fig. 1).. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to DNA-binding protein of Weininger et al. with the sequence-non-specific DNA-binding protein of Guagliardi et al. to thereby identify samples the highest homology to a probe having a disease-specific sequence for the expected benefit of accurately identifying and diagnosing the disease as taught by Guagliardi et al. (page 847, right column, lines 6-14).

13. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Weininger et al. (U.S. Patent No. 5,871,902, issued 16 February 1999) in view of Guagliardi et al. (Journal of Molecular Biology, 1997, 267: 841-848) and Stratagene (catalog, 1988, page 39).

Regarding Claim 13, Weininger et al. teach a kit for detecting hybridization between a probe and sample nucleic acid comprising a double-stranded DNA-binding protein (Claims 32-35) wherein their kit is for detection or analysis of a sample nucleic acid and they teach their nucleic aid sample detection and analysis methods comprises a fluorescently labeled probe (Column 1, lines 26-33 and Claim 2) but they do not teach the DNA-binding protein is sequence-non-specific. However, sequence-non-specific DNA-binding proteins were well known

in the art at the time the claimed invention was made as taught by Guagliardi et al. who teach a similar method of gene analysis comprising: hybridizing a probe nucleic acid and sample nucleic acid in the presence of a double-stranded DNA binding protein wherein the protein is sequence-non-specific i.e. strictly dependent on homology (Abstract) wherein said protein stabilizes complementary double-stranded DNA and promotes hybridization (Abstract) and whereby a single mismatch "severely reduces hybridization efficiency" (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made apply the sequence-non-specific DNA-binding protein of Guagliardi et al. to the DNA-binding of Weininger et al. to thereby differentiate between perfect-match and single mismatch hybridizations as taught by Guagliardi et al. for the obvious benefit of differentiating and detecting single-base mismatches known to be associated with clinically important diseases e.g. sickle cell anemia.

While Weininger et al and Guagliardi et do not specifically claim their kit comprises a labeled probe, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine all the method components taught by Weininger et al into the kit for the obvious benefits of providing the components in a convenient format.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Weininger et al and Gugaliardi et al into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. 2) The other service provided in a kit is quality control" (page 39, column 1).

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

15. No claim is allowed.

16. The examiner's Art Unit has changed from 1655 to 1634. Please address future correspondence to Art Unit 1634.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
October 23, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600